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Reading Comprehension in Pediatric Epilepsy

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Reading Comprehension in Pediatric Epilepsy

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Abstract

Reading Comprehension in Pediatric Epilepsy

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The purpose of this report is to explore the possible impact of childhood seizure disorders on reading comprehension abilities in a sample recruited from Dell Children's Medical Center. Due to the differently affected brain systems involved in generalized and focal epilepsy, analyses will focus on differential impact of specific seizure types on reading comprehension when controlling for full scale IQ. ANCOVA will be used to determine differences between generalized and focal epilepsy, and within focal epilepsy, between right- and left-lateralized seizure foci. Additional analyses will be conducted using multiple regression in order to examine variance accounted for by other contributing factors such as attention, working memory, age at onset, and medication.

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Introduction

Pediatric Epilepsy is the most prevalent chronic neurological disorder in childhood and adolescence, affecting approximately 1% of the population (Russ, Larson, & Halfon, 2012). Epilepsy is defined as two or more unprovoked epileptic seizures, which result from sudden electrical discharge of neurons in the brain. Seizures are often defined by the behavior of the child during the event, with different motor, auditory, visual, and cognitive symptoms providing information regarding the origin and progression of the abnormal electrical activity (Lee, 2010). Severity of seizures varies both between and within patients, with factors such as duration of seizure, age of onset, frequency, and type greatly influencing outcomes. Additionally, whether or not seizures are controlled with anti-epileptic drugs (AEDs) can produce further heterogeneity in seizure severity.

Children with epilepsy are at increased risk for behavioral, emotional, cognitive, and academic difficulties (Black & Hynd, 1995). While it is well known that children with epilepsy are more likely to display cognitive deficits, learning difficulties are often present as a result of specific cognitive disabilities rather than solely due to global intellectual impairment (Chaix et al., 2006; Reilly et al., 2014). Findings from previous studies indicate that academic achievement in childhood epilepsy is not affected in a uniform way (Reilly et al., 2014), and that distinct neurocognitive profiles emerge depending on seizure variables.

Reading comprehension is an essential component of accessing new information. As students progress from learning basic to complex concepts, greater importance is placed on learning from reading (Denton et al., 2015a). For students with reading difficulties, this transition presents a substantial barrier to learning and academic achievement. Children with reading difficulties have lower academic attainments and higher dropout rates in high school relative to their peers. Moreover, the impact extends into adulthood with significantly greater risk of unemployment, lower income, and poorer social and psychological adjustment associated with reading difficulties (Currie et al., 2017). Considering the substantial impact of reading comprehension in multiple systems throughout a person's life, understanding the development of appropriate comprehension skills in epilepsy populations is a necessary endeavor.

When controlling for IQ, individual differences in working memory significantly predict reading comprehension performance in nonepilepsy populations (Reilly et al., 2014). Given the high co-occurrence of executive function deficits and childhood epilepsy, it is reasonable to believe that a substantial number of children with epilepsy exhibit specific difficulty with reading comprehension. However, little is known regarding neurocognitive profiles of children with reading comprehension difficulties and epilepsy (Lah, Castles, & Smith, 2017). The purpose of this study is to determine whether specific types of epilepsy (e.g., generalized or focal) and lateralization of seizure focus differently impair reading comprehension abilities. Additionally, cognitive and seizure variables known to impact children with epilepsy will be examined to determine unique contribution in reading comprehension.

Integrative Analysis

Pediatric Epilepsy

Epilepsy is a neurological disorder that is characterized by recurrent unprovoked seizures due to excessive disorderly discharges of cerebral neurons (Lee, 2010). A seizure is defined as a brief surge of electrical activity in the brain resulting in a variety of clinical signs that are often accompanied by electroencephalographic (EEG) changes. These brief events typically last anywhere from a few seconds to several minutes. A person is considered to have epilepsy after two unprovoked seizures, though seizures may occur as secondary to another medical condition in which case the patient is not given an epilepsy diagnosis.

Epilepsy type is classified using three main features: where seizure activity begins in the brain, a person's level of awareness during the seizure, and other seizure features such as behavioral manifestation or motor involvement (ILAE, 2017). This classification system yields three main types of epilepsy. Focal seizures (previously called partial seizures) begin in one particular area or network of cells on only one side of the brain. Generalized seizures involve networks on both sides of the brain at onset. Finally, the category of unknown onset seizures is used for patients whose presentation does not provide enough EEG and behavioral evidence to be certain of seizure location. Additionally, some seizures begin as focal and progress to bilateral involvement. Within all subtypes of epilepsy, motor involvement (e.g., jerking or slackening of limbs) may or may not be indicated. While generalized seizures typically lead to a temporary loss of consciousness, focal seizures only occasionally impair awareness. In all cases, neuropsychological data used in conjunction with semiology (i.e., seizure symptomatology) can be especially useful in determining origin and progression of the abnormal electrical activity (Lee, 2010).

The underlying cause of an epileptic seizure is not well understood, however several theories have been proposed. One theory suggests that sodium, potassium, or calcium ion channels become disrupted (e.g., prolonged opening of channels) which leads to a chemical imbalance in the brain that results in seizure activity (Williams & Sharp, 2000). Another theory proposes that a seizure is the product of a problem with the membrane stabilizing mechanisms due to a disparity between inhibitory (i.e., deficient GABA and/or glycine) and excitatory (i.e., excessive glutamate and/or aspartate) neurotransmitters (Browne & Holmes, 2004). In addition, genetic influences play a factor in certain epileptic conditions and any traumatic brain injury may increase the risk of seizure activity.

Prevalence and Characteristics. Epilepsy is one of the most common neurological disorders of childhood (Black & Hynd, 1995) and therefore possibly the most frequent neurological disorder encountered by school psychologists. Although epilepsy can affect both adults and children, 50-70% of individuals who suffer from recurrent seizures have their first episode during childhood or adolescence (Dunn, 1988). According to the Center for Disease Control (CDC), in 2015 approximately 1.2% of the U.S. population reported active epilepsy, with an estimated 6.3 per 1,000 children under 18 diagnosed with a seizure disorder (Zack & Kobau, 2017).

NEUROCOGNITIVE FUNCTIONING. Children with epilepsy represent a heterogeneous group that varies along several dimensions. Presentation, progression, and underlying etiology may vary considerably from case to case (Black & Hynd, 1995). Epilepsy variables that can contribute to cognitive functioning include age of seizure onset, seizure frequency, and number of Anti-Epileptic Drugs (AEDs). Cognitive impairments are often associated with childhood epilepsy and can be a crucial complication of the condition contributing to negative psychosocial outcomes (Menlove & Reilly, 2015). An earlier age of seizure onset has been related to lower IQ scores and poorer prognosis for cognitive abilities overall, likely due to interference with the developmental trajectory of brain networks underlying cognition, which can result in both structural and functional impairments (Hermann et al., 2006; Menlove & Reilly, 2015). Additionally, epilepsy subtypes appear to reveal age-specific patterns in terms of underlying pathological processes (Black & Hynd, 1995). Although seizure frequency can often be complicated to measure and quantify, it has been found to be a contributor to both cognitive and behavioral problems (Berg et al., 2008; Rathouz et al., 2014), although longitudinal data tracking cognitive development from the time of diagnosis onwards is limited in both number and scope.

The use of AEDs can control seizures in approximately 70 to 80% of children with epilepsy (Williams & Sharp, 2000). Treatment with one AED is recommended when possible, because polytherapy is associated with an increased number of deleterious cognitive side effects (Fastenau, Dunn, & Austin, 2003; Lee, 2010). Cognitive side effects may include problems with attention, learning and memory, processing speed, and motor speed, as well as elevated hyperactivity, irritability, depressive symptomatology, aggressive behavior, sluggishness, and fatigue (Reith, Burke, Appleton, Wallace, & Pelekanos, 2004). Side effects are thought to be the product of an adjustment in metabolizing cerebral monoamines, endocrine functioning, drug-induced folate deficiency, or damage to the neurons (Julien, 2004). There are certain AEDs that show more side effects than others. For example, phenobarbital has been found to have a lasting effect on IQ scores in children (Sulzbacher, Farwell, Temkin, Lu, & Hirtz, 1999). Carbamezapine and phenytoin have been found to have deleterious effects on attention and reaction time. In addition, topiramate has been found to have negative effects on memory, attention, processing speed, language, and word finding tasks (Coppola et al., 2008; Lee, 2010).

Children and adolescents with epilepsy have an increased risk for cognitive, behavioral, emotional, psychiatric, and social deficits (Williams & Sharp, 2000), which have been found to occur more frequently in epilepsy than in other chronic medical conditions (Austin, Huberty, Huster, & Dunn, 1998). Studies have found variable results with regard to IQ scores in children with epilepsy, though it is generally agreed that children with epilepsy have poorer cognitive performance than their typically developing peers (Berg et al., 2013; Bourgeois, Prensky, Palkes, Talent, & Busch, 1983; Jokeit & Ebner, 2002). However, even if children with epilepsy have overall intellectual functioning that is in the normal range, specific deficits have been found consistently (Berg et al., 2013; Black & Hynd, 1995; Fastenau, Shen, Dunn, & Austin, 2008; Menlove & Reilly, 2015; Rathouz et al., 2014; van Iterson et al., 2015). In a longitudinal study by

Rathouz et al. (2014) the most vulnerable domains for children experiencing seizures involve motor and executive functions. Beginning at initial onset of seizures, children with generalized epilepsy were more adversely affected than those with focal epilepsy. Also, cognitive abnormalities were present at onset and remained mostly stable for 5-6 years, which was the length of the study at publication.

Executive function deficits have been found throughout the literature on pediatric epilepsy. Prevalence of Attention Deficit Hyperactivity Disorder (ADHD) among typical school populations is between 2-5%, whereas estimates range from 8-77% in children with epilepsy (Dunn et al., 2003). Though numbers of diagnosed ADHD in pediatric epilepsy vary considerably, this is a reflection of the wide range of approaches used to diagnose epilepsy-related cognitive difficulties. Executive functioning deficits are likely due to the disruption of subcortical or cortical mechanisms and occur in every epilepsy subtype (Fastenau et al., 2004). Interestingly, presence of ADHD in children with epilepsy is not significantly correlated with most epilepsy-related variables, including seizure focus, age at onset, and control of epileptic seizures (Zhang et al., 2012). Also, children with epilepsy differ from other ADHD samples in that a higher proportion are of the predominantly inattentive type and have an equal male to female ratio (Dunn et al., 2003). In addition to executive functioning and attention difficulties, children with epilepsy often experience problems with memory (Reilly et al., 2014). These deficits are consistent with findings comparing children with epilepsy only and children with epilepsy and other comorbities. Van Iterson et al. (2015) showed a distinct pattern of relatively spared verbal abilities when compared to performance abilities such as attention, memory, and processing speed. This differential impact of epilepsy occurs across comorbidities and seems independent of epilepsy-related variables. Even when children with epilepsy do not present with severe cognitive deficits, they may have a larger number of executive functioning problems and difficulties with academic achievement than non-epileptic children (Danguecan & Smith, 2017).

Academic Achievement. The relationship between specific cognitive deficits found in children with epilepsy and academic performance has received considerable attention (Black & Hynd, 1995). In fact, Berg et al. (2013) found that increased academic difficulties may precede the onset of epilepsy as evidenced by higher utilization of special education resources prior to diagnosis. Learning difficulties preceding diagnosis may be due to subclinical or unobserved seizure activity in young children. It is well established that children with epilepsy are at greater risk of experiencing difficulties in school compared to peers even when controlling for IQ (Berg et al., 2003; Black & Hynd, 1995; Fastenau, Shen, Dunn, & Austin, 2008). Impairments are most frequently seen in reading, spelling, arithmetic, and word recognition (Black & Hynd, 1995).

Academic underachievement is consistently found in large samples of children with epilepsy, even when children with intellectual disability are excluded (Dunn et al., 2010; Williams & Sharp, 1999). Fastenau et al. (2008) found that 41 to 62% of children with epilepsy had low achievement in at least one academic area. These difficulties in academic functioning can persist into adulthood and occur even in patients who are seizure free and no longer taking any AEDs. The origins of these academic problems in children with epilepsy are complex, and determining the underlying causes and contributions has proved difficult (Reilly & Neville, 2011). The factors that lead to academic difficulties in children with epilepsy are not well understood (Bourgeois, 1998; Seidenberg & Berent, 1992) and differ as a result of many variables (McNeils et al., 2005; Williams, 2003). Although some studies show higher rates of learning problems in children with focal epilepsy compared to generalized epilepsy (Stores & Hart, 1976; Zelnet et al., 2001), other studies have found no strong relations between seizure variables and achievement (Camfield et al., 1984; Schoenfel et al., 1999). Academic underachievement in pediatric epilepsy is therefore likely a result of interactions among neurological, seizure, medication, and social variables (Dunn et al., 2010; Reilly & Neville, 2011). Other influences that contribute to academic achievement in children with epilepsy are similar to those seen in the general population, such as preexisting learning disabilities, socioeconomic status and educational history of parents, and psychosocial problems within the family (Chaix et al., 2006).

Reading Comprehension

Reading is the primary means of knowledge acquisition in most domains (Freed et al., 2017). In Gough and Tunmer (1986)'s Simple View of Reading, reading comprehension consists of two dimensions: word reading and linguistic or language comprehension. Readers must be able to recognize the words on the page as well as connect those words to meaning (Hoover & Gough, 1990). Reading comprehension relies on a variety of factors such as an individual's word knowledge, knowledge of content areas, thinking and reasoning skills, and word reading ability (Gough, 1996). Researchers agree that both reading fluency as well as oral language proficiency are necessary for reading comprehension. While these two skills account for a large percentage of variance in reading comprehension ability, a great deal of research has focused on the remaining unexplained variance (Atkinson, Slade, Powell, & Levy, 2017).

Approximately 10 to 25% of poor readers who demonstrate adequate word recognition and decoding skills still show deficits in reading comprehension (Aaron, Joshi, & Williams, 1999; Catts et al., 2003; Leach Scarborough, & Rescorla, 2003). There are many theories regarding the direct and indirect paths influencing reading comprehension. While some refer to bottom-up and top-down processing, others use lower-level and higher-level processing to describe the same basic theory: reading comprehension consists of both word reading (i.e., decoding and fluency) and cognitive processes such as information integration, inference-making, and relating material to preexisting knowledge (Denton et al., 2015a; Denton et al., 2015b; Best, Floyd, & McNamara, 2012; Kim, 2015). The reliance on either lower-level or higher-level processing is highly dependent on reading experience, as those in lower grades typically exert the most effort on decoding and fluency, while those who have mastered basic reading skills are free to concentrate on higher-level competencies (Best et al., 2012). Therefore, as demand for learning from text and text difficulty increases, distinct differences in underlying mechanisms leading to reading difficulties emerge.

Many of the higher-level processing skills necessary for adequate comprehension can be related to executive functioning abilities. Executive functions are described as a collection of interconnected processes which are responsible for goal-directed behavior and the planning process of how to achieve those goals (Lezak, 1982; Stuss & Benson, 1986). They include the control and organization of multifaceted cognitive processes that allow an individual to create strategies, solve problems, and adjust behaviors as a result of new information. Executive functions are theorized to include the following major components: anticipation and deployment of attention, impulse control and self-regulation, initiation of activity, working memory, mental flexibility and utilization of feedback, planning ability and organization, and selection of efficient problem-solving strategies (P. Anderson, 2002; V. Anderson & P. Anderson, 2008; V. Anderson, Anderson, Northam, Jacobs, & Catroppa, 2001). Indeed, Arrington, Kulesz, Francis, Fletcher, and Barnes (2014) reported significant direct effects of working memory, sustained attention, and cognitive inhibition on reading comprehension, but not decoding. Cromley & Willis (2016) found that good comprehenders have more strategies available to them and use these strategies in a constructively responsive manner. The direct and inferential mediation (DIME) model of reading comprehension includes background knowledge, inference, strategies, vocabulary, and word reading all used in conjunction to make meaning of text (Cromley & Willis, 2016). While foundational reading skills are needed in order to access the given information, individuals must also be able to flexibly allocate and re-allocate attention in order to form a comprehension mental model of the text (Denton et al., 2015a). Additionally, mental representation of text requires integration of relevant background knowledge, also referred to as crystallized intelligence (Best et al., 2012; Lesaux & Harris, 2017).

In addition to strategy use and attention allocation, children with reading disorders have been found to demonstrate difficulties with both verbal and visual working memory tasks (Freed, Hamilton, & Long, 2017; Reiter, Tucha, & Lange, 2005). Working memory may assist in reading comprehension by allowing an individual to employ skills such as decoding, recalling familiar word sounds, and making inferences, all at the same time. Also, working memory is necessary for keeping in mind what the first half of the sentence or passage said while reading the second half of the sentence or passage. Other higher-level processing skills found to contribute to reading comprehension include motivation (Cartwright, Marshall, & Wray, 2016), processing speed, and comprehension monitoring (Atkinson et al., 2017). Those with intact reading comprehension abilities use cognitive strategies such as planning and metacognitive strategies such as paraphrasing and self-monitoring more than those who do not have intact reading comprehension abilities (Atkinson et al., 2017; Denton et al., 2015b; Lesaux & Harris, 2017).

NEURAL CORRELATES OF READING COMPREHENSION

One can assume that such a complex cognitive process includes an equally complex orchestra of neural activity. Studies using functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have attempted to identify brain areas responsible for accurate reading comprehension (Aboud, Bailey, Petrill, & Cutting, 2016; Alcauter et al., 2017; Buchweitz, Mason, Tomitch, & Just, 2009; Friederici, Rueschemeyer, Hahne, & Fiebach, 2003; Horowitz-Kraus et al., 2015; Liu et al., 2010; Moss, Schunn, Schneider, McNamara, & VanLehn, 2011; Newman, Malaia, Seo, &

Cheng, 2013; Smallwood et al., 2013; Vogel et al., 2013; Welcome & Joanisse, 2014; Yarkoni, Speer, & Zacks, 2008). It is well established that language networks seen in receptive and expressive language ability are involved in lower-level reading processes such as decoding. This typically left-lateralized network involves Broca's area (i.e., left inferior frontal gyrus) and the word form area (i.e., fusiform gyrus) as well as association areas (e.g., middle temporal gyrus and temporal pole) required for phonological processing (Aboud et al., 2016). To a lesser degree, the dorso-lateral prefrontal cortex, an area traditionally associated with working memory (WM), is involved in word-level processes. Less established are networks responsible for higher-level processes such as comprehension monitoring, inference, and mental representation of text.

As may be anticipated given the theoretical underpinnings of reading comprehension, brain imaging studies confirm that reading comprehension is supported by a temporo-frontal network with distinct areas specialized for semantic and syntactic processes, as well as additional recruitment of areas responsible for executive functioning (Alcouter et al., 2017; Moss et al., 2011; Vogel et al., 2013). Higher-level processes seem to involve several consistent areas. The posterior cingulate cortex (PCC) has been shown to be active during comprehension tasks but not single word reading across several fMRI studies (Binder et al., 2009; Newman et al., 2013; Yarkoni et al., 2008). The PCC is thought to be involved in a number of memory processes including semantic, episodic, and visuo-spatial memory (Newman et al., 2013). It has been suggested that this area may be responsible for producing a mental model of the text (Yarkoni et al., 2008). Smallwood et al. (2013), however, posited that the PCC is activated during comprehension due to activation of the default-mode network (DMN). The function of the DMN is not clearly established, and most research points to its involvement in "mind-wandering" or off-task thoughts. Due to the PCC's role in memory, it is possible that activation of the DMN is multimodal when reading, both contributing to unrelated thoughts and providing necessary information retrieval (Binder and Desai, 2011). Similarly, the left angular gyrus, which supports global semantic and conceptual integration but is also part of the DMN, is active during comprehension tasks (Aboud et al., 2016).

Additional areas consistently indicated in reading comprehension brain imaging studies are those thought to be responsible for WM and attention. The prefrontal cortex (PFC) has been noted to play an important role in executive functioning and is activated in many cognitive tasks, including reading comprehension. The ventro-medial and dorso-medial PFC is activated bilaterally during self-explanation of text and learning from text (Moss et al., 2011). Although the frontal lobes have been shown to play a pivotal role in executive functioning, recent evidence suggests that the entire brain may be necessary for adequate executive functioning abilities. The neural systems that are involved with executive functions are interrelated and connected and therefore the prefrontal cortex is dependent on connections to many areas of the brain, including the brain stem, cerebellum, occipital, temporal, and parietal lobes, as well as the limbic and subcortical regions (Alexander & Stuss, 2000). Indeed, studies have found subcortical areas such as the striatum in the basal ganglia and thalamus to be important for comprehension adequacy (Alcauter et al., 2017; Friederici et al., 2003; Smallwood et al., 2013). These findings are further emphasized when examining the neural activity of struggling readers.

NETWORKS INVOLVED FOR STRUGGLING READERS. Children with reading difficulties show different patterns of brain activity during reading comprehension tasks (Horowitz-Kraus et al., 2015). While typical readers show primarily left-lateralized language area activation and relatively small contributions from the right hemisphere and prefrontal cortex (George et al., 1999; Xu et al., 2005), struggling readers show additional right-hemisphere recruitment and significant reliance on PFC. Importantly, reading comprehension seems to involve both hemispheres of the brain in both average readers and poor readers, but in those with comprehension deficits increased right-hemisphere involvement is present. Readers with poor comprehension recruit significantly more voxels of analogous language areas in the right hemisphere, indicating a need for additional neural resources in order to carry out comprehension processes. Given the strongly left-lateralized activation during word reading only, this finding lends physiological support for a distinction between different types of reading comprehension deficits: those resulting from deficient lower-level processes, and those resulting from deficient higher-level processes (Horowitz-Krause et al., 2015).

READING COMPREHENSION IN EPILEPSY

Compared to typical children matched on age, gender, and level of education, children with epilepsy have been found to perform significantly lower in reading (Black & Hynd, 1995). Mitchell, Chavez, Lee and Guzman (1991) found that 38% of children with epilepsy were underachieving in reading comprehension after controlling for IQ, the highest percentage of any academic domain for this sample. Performance was significantly more impaired for comprehension of a paragraph than for reading words in isolation. Harrison, Cross, Harkness, and Vargha-Khadem (2013) found that 47% of children with focal epilepsy had impaired reading comprehension when controlling for IQ. Reading comprehension was significantly lower than all other academic areas. Considering the multiple neural correlates of reading comprehension and the neurological impact of pediatric epilepsy, recent studies have sought to better understand the influence of seizures on this specific cognitive deficit (Chaix et al., 2006; Currie et al., 2017; Ebus, Overvliet, Arends, & Aldenkamp, 2011; Harrison et al., 2013; Jones, Siddarth, Gurbani, Shields, & Caplan, 2010; Lah, Castles, & Smith, 2017; Lah & Smith, 2014).

Language Lateralization. It is widely accepted that neural substrates for language including speech and reading are typically well lateralized and regionally specific during the first decade of life (Duchowny, 2007). However, in pediatric epilepsy, language lateralization can by disrupted by underlying neuropathology (Berl et al. 2005; Gaillard et al., 2007; Yuan et al., 2006). This disruption can modify classical assumptions of language localization and networks, with a potential contribution of PFC to language competence over and above that for typically developed children. Berl et al. (2005) found that both children with right-lateralized and children with left-lateralized seizure foci had greater right-hemisphere activation during language processing tasks than typically developing children. Chaix et al. (2006) examined the role of laterality in TLE as well as differences between generalized, TLE, and rolandic (or BECTS) epilepsy subtypes for various reading skills. They found a significant difference between type only for comparisons between TLE and BECTS, with TLE children showing greater deficits in reading speed and comprehension. No significant differences were found between type for phonological processing and rapid naming. Laterality of seizure focus for TLE showed a significant effect, with left-lateralized patients scoring well below right-lateralized patients. Caplan et al. (2009) found a wider range of linguistic deficits in older epilepsy subjects, indicating an age-related rise in vulnerability to linguistic deficits and differential effects of seizure variables. Considering typical neurodevelopmental trajectory, it can be hypothesized that this increase in language impairment may be related to underlying executive functioning disruption. Difficulties encountered by the child with epilepsy may therefore be associated with subtypes of the disorder, and those with reading comprehension problems may have difficulty with executive functioning more so than language (van Iterson et al., 2015).

Executive Functioning. While there has been evidence that some executive skills may develop in infancy, the more complex skills such as planning and problem solving continue to develop until late adolescence. Epilepsy that begins during childhood likely disrupts these developing executive functioning skills. Therefore, it is not surprising that executive dysfunction has been found to be present across all childhood epilepsy types. For example, memory problems have been reported in children with frontal lobe, temporal lobe, and absence (generalized) epilepsies (Nolan et al. 2004).

Executive dysfunction has also been related to age at seizure onset, seizure frequency, and number of AEDs (Hoie, Mykletun, Waaler, Skeidsvoll, & Sommerfelt, 2006; Williams & Sharp, 2000). Hoie et al. (2006) found that an earlier age of seizure onset and increased seizure frequency were significantly associated with more perseverative errors than patients with a later age of seizure onset. In addition, in a sample of people with temporal lobe epilepsy, problem solving was found to be worse in patients with an earlier age of seizure onset than those with a later age of onset (Hermann et al., 2006). Studies evaluating functional connectivity of children with epilepsy find that they exhibit a suboptimal network arrangement with fragmented executive functions, and less-organized networks throughout cognitive domains (Kellermann, Bonilha, Lin, & Hermann, 2015). Shamshiri et al. (2017) found that even in a task with low cognitive demand, significant differences exist between network connectivity of typically developing children and those with epilepsy, with compromised connectivity in the epilepsy group. In a study comparing children with frontal lobe epilepsy (FLE) and temporal lobe epilepsy (TLE), no clear-cut mapping of function onto structure was found, with both types of focal epilepsy involving networks spanning brain hemispheres (Smith, 2016).

Summary

Children with epilepsy are at increased risk for cognitive deficits and specific learning disabilities. Distinct academic deficits may be associated with subtypes of epilepsy disorders; however, reading comprehension deficits have yet to be compared across epilepsy subtypes. Reading comprehension is a complex process necessary for higher learning that involves multiple neural networks, specifically language and executive functioning networks. Children with epilepsy not only have differently impaired language functioning due to underlying neuropathology and lateralization of cortical dysfunction, but also have compromised executive functioning across epilepsy subtypes. Further research is warranted to explore subtype specific deficits in reading comprehension, as well as risk factors for developing learning disorders in reading comprehension for children with epilepsy.

Proposed Research Study

Statement of Problem

Emerging research has begun to explore the impact of epilepsy on reading comprehension in adults and children (Vanasse, Beland, Carmant, & Lassonde, 2005; Chaix et al., 2006; Ebus et al., 2011; Malfait et al., 2015; Currie et al., 2017; Lah et al., 2017). Important variables have been identified, including age at seizure onset, overall global impairment, and use of Anti-epileptic Drugs (AEDs). However, the majority of these studies have either looked at children with epilepsy without isolating specific epilepsy sub-types, or have focused primarily on Temporal Lobe Epilepsy (TLE). Additionally, many studies had limited sample sizes preventing methodologically sound comparison between sub-types. Previous studies have shown that distinct neurocognitive profiles emerge depending on the sub-type of epilepsy and the underlying brain structures involved (Fastenau et al, 2008; Menlove & Reilly, 2015; Rathouz et al., 2014). Further attention should be given to how reading comprehension differs among these epilepsy sub-types in an effort to provide more accurate treatment planning and, potentially, to aid in the diagnostic process.

Statement of Purpose

The purpose of this proposed study is to explore any differential impact of epilepsy sub-types on reading comprehension abilities. Sub-types will be divided into three groups: generalized epilepsy, focal epilepsy with temporal lobe involvement (TLE), and focal epilepsy with frontal lobe involvement (FLE). Within focal epilepsy, two subgroups, those with right-lateralized seizure foci and those with left-lateralized seizure foci, will be compared to further understand the involvement of supporting brain networks. Additionally, known components leading to reading difficulties in school and clinical populations will be included to assess their possible contribution to reading comprehension deficits for children with epilepsy. Specifically, demographic and seizure variables (e.g., SES, age at onset, and number of AEDs) will be examined, along with cognitive variables (e.g., verbal knowledge, reading decoding, working memory, and attention). It is hypothesized that both epilepsy type and lateralization of seizure focus have an effect on reading comprehension and that attention deficit will predict reading comprehension ability after controlling for potentially confounding demographic, seizure, and basic reading variables.

Research Questions and Hypotheses

Research question 1. In children and adolescents with seizure disorders, does epilepsy type (generalized vs. focal; TLE and FLE) differently affect reading comprehension?

Hypothesis 1. There will be a significant main effect of epilepsy type on reading comprehension performance. Specifically, when controlling for IQ, the focal epilepsy group will show significantly poorer performance on a measure of reading comprehension than those with generalized epilepsy. However, within focal epilepsy sub-type (FLE, TLE), no significant differential effect is expected.

Rationale. While Rathouz et al. (2014) found that children with generalized epilepsy showed greater executive functioning impairment than those with focal epilepsy, no significant difference was found for reading skills. Other studies have found distinct weakness in reading comprehension for children with TLE as compared to those with generalized epilepsy (Chaix et al., 2006; Lah et al., 2017; Lah & Smith, 2014), but did not include FLE in their samples. Considering the underlying neural networks involved in FLE and TLE, disruptions to these networks are likely to impact both language comprehension and supporting executive function processes necessary for reading comprehension.

Research question 2. Does lateralization of seizure focus differently affect reading comprehension in children with Focal Epilepsy?

Hypothesis 2. There will be a significant effect of lateralization of focus on reading comprehension. When controlling for IQ and decoding ability, those with right-hemisphere foci will show poorer performance on a measure of reading comprehension.

Rationale. Little research has been conducted on the effect of seizure focus topography on academic achievement. Chaix et al. (2006) examined lateralization of seizure focus in children with TLE, and found that those with left hemisphere foci had lower reading skills than children with right hemisphere foci. Considering the increased likelihood of atypical language in patients with left hemisphere seizure focus (Berl et al., 2005), it is reasonable to assume that lower reading skills are a result of disruption to language networks and therefore patients with left-lateralized foci are at increased risk of difficulties. However, previous studies have not examined the effect of seizure focus on reading comprehension when controlling for basic reading skills. It is hypothesized that when controlling for decoding ability, right hemisphere foci will have a greater impact due to impaired higher-level processes involving the DMN and other executive function networks (Oser et al., 2014).

Research question 3. Which variables of interest (age at onset, number of AEDs, SES, working memory, attention, decoding and verbal knowledge) explain the most variance in reading comprehension among children with epilepsy?

Hypothesis 3. Demographic and seizure variables of age at onset, number of AEDs, and SES will account for a significant amount of the variance in reading comprehension performance. Cognitive variables of IQ and decoding will account for a significant amount of variance unexplained by demographic and seizure variables. Attention will account for a significant amount of variance unexplained by cognitive, demographic, and seizure variables. Working memory will not account for a significant amount of the variance in reading comprehension performance beyond that accounted for by cognitive, demographic, and seizure variables.

Rationale. Research on learning disorders has consistently documented contribution of SES in academic achievement, especially in regard to language and reading abilities (Barnes, Ahmed, Barth, & Francis, 2015; Guajardo & Cartwright, 2016; Kieffer, Vukovic, & Berry, 2013). Seizure variables such as age at onset and number of AEDs, while often found to contribute to increased cognitive impairment and poorer academic achievement, have been inconsistently implicated in the area of reading comprehension (Guimaraes et al., 2007; Smith, Bajomo, & Pal, 2015; Smith et al., 2012;

Oser et al., 2014). Reading decoding and crystallized knowledge are found to contribute significantly to reading comprehension (Bednarz et al., 2017; Breaux et al., 2017; Evans, Floyd, McGrew, & Leforgee, 2002; Perfettim Marron, & Foltz, 1996). Less understood is the contribution of various executive functions, specifically working memory and attention (Chen, Schneps, Masyn, & Thomson, 2016; Georgious & Das, 2016; McVay & Kane, 2012; Sesma, Mahone, Levine, Eason, & Cutting, 2009; Stern & Shalev, 2013). Considering the high co-occurrence of attention difficulties and pediatric epilepsy (Gascoigne et al., 2017), attention is likely to be a significant variable in reading comprehension when controlling for other contributing variables.

Method

Participants

Participants in this study will include approximately 160 children and adolescents with active epilepsy. Participants will be recruited through the Epilepsy Program at Dell Children's Hospital in Austin, Texas. Participants will be between the ages of 6 to 16 so that all participants can be evaluated with reading comprehension measures.

Inclusion criteria will be: (i) aged 6 to 16 years old at the time of their participation in the study, (ii) identified as having a seizure disorder, as verified by EEG and neurologist diagnosis, (iii) generalized or focal seizures with documented focus location as determined by EEG, semiology, and neurologist diagnosis. Participants with multiple epilepsy types will be excluded from this study. Participants will be considered eligible to participate if they meet all inclusionary criteria and have completed measures of IQ and reading comprehension.

Instruments

Participants will be administered a full neuropsychological assessment including measures of IQ and reading comprehension. The measures are described below, along with their psychometric properties and purposes in this study.

Reading Measures. *Woodcock-Johnson IV Test of Achievement (WJ-IV).*

The Woodcock-Johnson IV Test of Achievement (WJ-IV; Schrank, Mather, & McGrew, 2014) contains subtests that measure separate domains of reading ability. For the purposes of the present study, two subtests will be used in analysis, Letter-Word

Identification and Passage Comprehension. The Letter-Word Identification subtest assesses the ability to name letters, identify phoneme sounds, and read words varying in difficulty from sight words to multisyllabic words. The median reliability for this measure was .91 in the standardization data (Schrank, Mather, & McGrew, 2014). The Passage Comprehension subtest assesses sentence-level comprehension through the use of a cloze procedure, requiring students to fill in missing words based on overall context. This measure will be used as the dependent variable of interest and has a median reliability of .83.

Full Scale IQ. *Wechsler Intelligence Scale for Children – 5th Edition (WISC-V).* The Wechsler Intelligence Scale for Children – Fifth Edition (WISC-V; (Wechsler, 2014) is a widely used measure of cognitive functioning with an age range of 6:0 to 16:11. The core battery consists of ten subtests, seven of which comprise the overall IQ and three supplemental subtests that are not included in the overall IQ. The core battery takes approximately one hour to administer and provides both a Full Scale IQ (FSIQ) and index scores (e.g., Fluid Reasoning, Processing Speed) used to assess cognitive abilities across several domains. This study will use the FSIQ as a measure of overall cognitive ability, as well as the score from two subtests that comprise the Working Memory Index (WMI).

Working Memory. The Working Memory Index (WMI) from the WISC-V includes Digit Span and Picture Span. Digit Span is a verbal working memory task, consisting of Digit Span Forward, Backward, and Sequencing. In each condition, participants are asked to repeat a string of digits. Digits are repeated as presented, in the opposite order than presented, and placed in numerical order upon repetition. Each condition is discontinued when participants fail both trials of a given set, typically differing by amount of numbers presented. Performance on each condition is combined to yield a single score for Digit Span. The reported internal consistency for this subtest from the normative sample was 0.91. Picture Span, a visual working memory task, requires participants to view sets of pictures, then point to those items in the order presented from an array of other items. The reported internal consistency for this subtest was 0.85. Digit Span and Picture Span are then combined to produce and overall WMI composite score, which will be included in the multiple regression as a cognitive variable.

Attention. *Behavior Rating Inventory of Executive Function (BRIEF).* The Behavior Rating Inventory of Executive Function, Parental Report (BRIEF-PR; Gioia, Isquith, Guy, & Kenworthy, 2000) is a parent rating scale designed to reflect various components of a child's daily executive functioning. Two global scales are produced, the Behavioral Regulation index (BRI) and the Metacognitive Index (MI). Cronbach alpha ranges from .80-.98 for reported internal consistency, and test-retest reliability across clinical scales for a normative sub-sample was $r = 0.81$ for an average interval of two weeks (Gioia et al., 2000). Considering the high demand on metacognitive skills found in reading comprehension literature, the MI will be used in this study to measure attention as a cognitive variable. Reliability estimates for the MI range from 0.83 – 0.90 in a sample of children with Epilepsy (MacAllister, Vasserman, Rosenthal, & Sherman, 2014), with acceptable convergent validity in a clinical sample of children with and without ADHD (McCandless & Laughlin, 2007).

PROCEDURE

Epilepsy Type. Epilepsy type will be extracted from each participant's medical records, with generalized or focal epilepsy diagnosed by their neurologist and verified by EEG monitoring, fMRI, and neuropsychologist interpretation. Only participants with determinable epilepsy types will be included in this study. Participants will be coded according to subtype: generalized epilepsy, FLE, or TLE.

Seizure Focus location. Seizure focus location will be determined using EEG monitoring, fMRI, and neuropsychologist interpretation. Only participants with clearly lateralized foci will be included in this study. Participants will be coded as either right- or left-lateralized focus.

Approval by human subjects committee. This study will be conducted in compliance with ethical standards set forth by the American Psychological Association and the University of Texas at Austin. As such, all research materials and procedures will be approved prior to the start of data collection by the Departmental Review Committee within the Department of Educational Psychology and by the Institutional Review Board of the University of Texas at Austin.

Recruitment of participants. Participants will be recruited through the Pediatric Neuropsychology Clinic at Dell Children's Medical Center in Austin, Texas. Children diagnosed with epilepsy by their neurologist and referred for a neuropsychological evaluation that meet the inclusionary criteria will be invited to participate.

Consent. Parents or guardians of participants will receive a copy of the consent form and will be encouraged to discuss any concerns. All participation in this study will be voluntary, with ability to discontinue participation at any time. Verbal assent will be discussed with child participants during their intake interview with the neuropsychologist supervising their case and noted in their file.

Data Collection. Children whose parents have given consent for participation, who assent to participate in the study, and who meet inclusion and eligibility criteria for this study will be participants. Informed consent and assent will be obtained, and neuropsychological evaluation will follow as part of routine medical care within the DCMC Epilepsy Clinic. All evaluations will take place one-on-one in a quiet, private room in either the Pediatric Specialty Services Clinic or Epilepsy Monitoring Unit of DCMC. Children will be given breaks as needed determined by the administering psychometrist or practicum student.

DATA ANALYSES AND EXPECTED RESULTS

The purpose of this study is to examine the differential impact of epilepsy type (generalized or focal, right- or left-lateralized) on reading comprehension as well as explore predictors of reading comprehension achievement among children and adolescents with pediatric epilepsy. Data will be analyzed using analysis of covariance and multiple regression.

PRELIMINARY ANALYSES. A power analysis was conducted using G*Power software to determine the number of participants needed to detect a significant effect (Faul, Erdfelder, Buchner, & Lang, 2009). A power analysis for detecting significance of a moderate effect size (overall R2) with a power of 0.80 at an alpha of 0.05 with six predictor variables indicated a need for 98 participants. A power analysis for detecting significance of a moderate effect size with a power of 0.80 at an alpha of 0.05 with two covariates and two groups in an analysis of covariance indicated a need for 128 participants. Power analysis for detecting significance of a moderate effect size with a power of 0.80 at an alpha of 0.05 with one covariate and three groups in an analysis of covariance indicated a need for 158 participants.

Prior to conducting the formal analysis of the data, statistical inference assumptions associated with multiple regression and analysis of covariance will be assessed. Descriptive statistics, including means, standard deviations, ranges, and minimum and maximum values will be computed and analyzed for each variable. Variables will be checked for normality and data will be examined for any potential outliers. Linearity will be determined by examining scatterplots. Normal distribution of residuals will be confirmed using a residual and predicted value plot. Covariates have been found to have good reliability, and linearity of the relations between covariates and reading comprehension will be verified. Finally, equality of regression slopes in analysis of covariance will be examined.

TEST OF RESEARCH QUESTIONS. Analysis of covariance will be conducted to determine any differential effect on reading comprehension for epilepsy sub-type and lateralization of seizure focus. In the first analysis, three groups (generalized, FLE, TLE) will be analyzed with reading comprehension as the dependent variable and FSIQ as the covariate. Main effects of seizure type will be examined and post-hoc tests will be conducted to determine direction of effect. A second analysis of covariance will be conducted to determine differential effect of seizure focus lateralization by separating FLE and TLE participants into two groups by hemisphere of seizure focus. Again, reading comprehension will serve as the dependent variable. Covariates of IQ and reading decoding will be included to determine differential impact focus lateralization on reading comprehension over and above basic reading ability.

Linear multiple regression analyses will be conducted to examine the relations between epilepsy subtype and reading comprehension, controlling for age at seizure onset, number of AEDs, and SES.

The first block of the regression model will contain known variables contributing to global impairment in children with epilepsy. Reading comprehension will be regressed on age at seizure onset, number of AEDs, and SES. Variables necessary for lower-level reading processes, reading decoding and IQ, will be included in the second block. Executive functioning variables, working memory and attention, will be entered into the final block. The p-value associated with the change in R^2 will be examined to determine which variables explain a statistically significant amount of variance in reading comprehension for children with epilepsy at an alpha level of 0.05.

Hypothesis 1. There will be a main effect of epilepsy type on reading comprehension when controlling for FSIQ and reading decoding. It is hypothesized that children with FLE will score significantly lower on a measure of reading comprehension when compared to generalized epilepsy. It is hypothesized that children with TLE will score significantly lower on a measure of reading comprehension when compared to generalized epilepsy. It is also hypothesized that no significant difference will be detected between FLE and TLE.

Hypothesis 2. There will be a main effect of lateralization of seizure focus on reading comprehension when controlling for IQ and reading decoding. It is hypothesized that those with right-hemisphere foci will score significantly lower on a measure of reading comprehension when compared to those with left-hemisphere foci.

Hypothesis 3. Attention will account for a significant amount of variance in reading comprehension after controlling for cognitive variables (reading decoding and IQ), seizure variables (age at onset, number of AEDs), and demographic variables (SES). It is hypothesized that elevated attention deficit will predict poorer performance on a measure of reading comprehension.

Discussion

Limitations

The proposed study has several limitations, including the lack of control or comparison group. While a review of the literature informed the selection of measures and hypotheses based on previous studies with typically developing children, the present study would further strengthen its conclusions regarding the impact of epilepsy on reading comprehension if participants were matched with non-epilepsy peers. Further, clinical heterogeneity in children with epilepsy is one of the main methodological biases in studies on the impact on cognitive development (Chaix et al., 2006) and the proposed sample is likely to suffer this bias as well. Though epilepsy sub-types will be examined, a great deal of variation exists within sub-types from underlying neuropathology to treatment and severity.

One area that may have a noticeable impact on reading comprehension in both typical and clinical populations is availability of and access to best-practices reading instruction. Very little data is collected on type of reading instruction received for children undergoing treatment for epilepsy, though recommendations for placement in special education or small-group instruction is often found. Additional demographic data that may contribute to reading comprehension outcomes include Race/Ethnicity and presence of comorbidities. The sample size of this study limited the number of predictors included in analysis, and therefore a population-based sample may be necessary to include a larger set of measures and variables.

SUMMARY AND IMPLICATIONS

The proposed study is an important step toward better understanding of specific learning deficits in children with epilepsy. A large number of children with epilepsy struggle with reading comprehension, which increases risk of poorer outcomes in academic achievement. Through early identification of increased vulnerability to reading difficulties, children with specific sub-types of epilepsy may have a greater chance at remediation. Research on both reading theory and reading neurobiology confirms two necessary areas for accurate reading comprehension: lower-level processes that are localized in the language center of the brain, and higher-level processes that in include a broad network of brain areas, especially those related to executive function.

Given the frequency of executive functioning deficits in children with epilepsy, further investigation into how reading comprehension differs in the presence of distinct neuropathology may provide greater insight into the brain basis of reading comprehension. Many treatment programs for reading comprehension deficits have incorporated an executive functioning component into their interventions, including those designed for remediation of traumatic brain injury (Griffiths, Sohlberg, Kirk, Fickas, & Biancarosa, 2016; Martinussen & Mackenzie, 2015; McMaster, et al., 2015). Findings from the present study may further strengthen this approach to reading comprehension intervention.

Neuropsychological testing is a key component of the diagnostic process for children with epilepsy. Discrepancies between verbal and non-verbal abilities, for instance, can help determine laterality of seizure focus due to the typically left-lateralized language network. Similarly, pronounced difficulties with aspects of motor or sensory perception can help determine whether anterior or posterior areas of cortex are impaired. This information not only helps with diagnosis, but also with treatment planning and providing early intervention in academic areas likely to be affected. There is a paucity of research on the impact of lateralization of seizure focus on academic achievement, and no studies to date have investigated how different seizure topography contributes to reading comprehension. The present study seeks to fill this gap, increasing our understanding of how to support children with seizure disorders.

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